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*Published in:*  
International Journal of Surgery

*DOI:*  
[10.1016/j.ijisu.2015.12.008](https://doi.org/10.1016/j.ijisu.2015.12.008)

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2016

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Boersema, G. S. A., Vakalopoulos, K. A., Kock, M. C. J. M., van Ooijen, P. M. A., Havenga, K., Kleinrensink, G. J., Jeekel, J., & Lange, J. F. (2016). Is aortoiliac calcification linked to colorectal anastomotic leakage? A case-control study. *International Journal of Surgery*, 25, 123-127. <https://doi.org/10.1016/j.ijisu.2015.12.008>

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Original research

# Is aortoiliac calcification linked to colorectal anastomotic leakage? A case-control study



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## HIGHLIGHTS

- Left-sided colon anastomoses are associated with a higher leakage risk.
- Correlation of abdominal atherosclerotic calcifications and leakage was investigated.
- No association is found between the calcium score/volume and anastomotic leakage.
- Visualization of the collateral network around the anastomosis may be helpful.

## ARTICLE INFO

### Article history:

Received 21 October 2015

Received in revised form

16 November 2015

Accepted 4 December 2015

Available online 14 December 2015

### Keywords:

Calcium volume

Calcium score

Anastomotic leakage

Prognostic factor

Colorectal surgery

## ABSTRACT

**Background:** Anastomotic leakage in bowel surgery remains a devastating complication. Various risk factors have been uncovered, however, high anastomotic leakage rates are still being reported. This study describes the use of calcification markers of the central abdominal arteries as a prognostic factor for colorectal anastomotic leakage.

**Methods:** This case-control study includes clinical data from three different hospitals. Calcium volume and calcium score of the aortoiliac tract were determined by CT-scan analysis. Cases were all patients with anastomotic leakage after a left-sided anastomosis ( $n = 30$ ). Three controls were randomly matched for each case. Only patients with a contrast-enhanced pre-operative CT-scan were included.

**Results:** The measurements of the calcium score and calcium volume of the different trajectories showed that there was one significant difference with regard to the right external iliac artery. Multiple regression analysis showed a significant different *negative* odds ratio of the presence of calcium in the right external iliac artery.

**Conclusion:** This study demonstrates that calcium volume and calcium score of the aortoiliac trajectory does not correlate with the risk of colorectal anastomotic leakage after a left-sided anastomosis.

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## 1. Introduction

The occurrence of anastomotic leakage (AL) after colorectal surgery remains a severe complication leading to high morbidity and mortality. Literature has identified the main risk factors for colorectal anastomotic leakage: male gender, pre-operative

radiotherapy, low anastomosis (<10 cm from the anal verge), high BMI, high comorbidity, ligation above the left colonic artery, advanced age, and a history of vascular disease [1–8]. Despite the accumulation of knowledge and the improvements brought by novel surgical techniques, the incidence of AL for left sided anastomosis remains high, in the literature leakage rates of approximately 8–18% are mentioned [4,9–14].

Smoking, high BMI, hypertension and hypercholesterolemia are risk factors for AL but also for atherosclerosis [15]. An atherosclerotic plaque is made up of fat, cholesterol, and calcium, hardening

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and narrowing the arteries with limitation of oxygen-rich blood flow. Atherosclerosis is correlated with tissue ischemia and anastomotic leakage caused by poor microcirculation [16–21]. The calcium in the atherosclerotic plaques in the arteries can be scored on computed tomography (CT) by dedicated scoring software. The Agatston calcium score, which is the most validated and most frequently used scoring system as a predictor in previous studies, is the product of the density factor and the area of the calcified plaques ( $\text{mm}^2$ ) [22]. The calcium volume score represents an actual volume of calcium in the artery and reduces calcium measurement variability between scans [23]. The presence of calcium is considered to stabilize the plaque, which decreases the chance of plaque rupture and subsequent ischemic disease [24]. Nevertheless, several studies have shown a correlation between the calcium score and cardiac events [22,25]. Patients with high Agatston scores have a higher frequency of cardiac adverse events whereas a calcium score of zero portrays a very low risk for short-term and midterm cardiac events [26,27]. A correlation has also been described between higher Agatston score, calcium mass, and calcium volume in various abdominal arteries and the risk of AL after colorectal surgery [28].

In this case-control study we investigated whether the calcium score using Agatston or volume score also can be used as a predictive factor for left-sided colorectal anastomotic leakage, based on enhanced CT measurements.

## 2. Methods

### 2.1. Study population

During 2009 and 2011 all patients undergoing a primary left sided colorectal anastomosis, operated by colorectal surgeons or surgical residents, who preoperatively received a contrast enhanced abdominal CT-scan with a 5 mm slice thickness, were included. Data was obtained from the following teaching hospitals; the Erasmus University Medical Center Rotterdam (EMC), Albert Schweitzer hospital Dordrecht (ASD), and the University Medical Center Groningen (UMCG). In this retrospective case-control study cases were patients who had radiographically confirmed anastomotic leakage within 30 days postoperatively. At least 3 controls per case were randomly selected and matched by sex, age, ASA classification, diverting stoma and operation, some cases having 4 controls.

Data collection included age, sex, body mass index (BMI), American Society of Anaesthesiologists (ASA) score, medication use, smoking, alcohol use, operative procedure, postoperative complications and postoperative course.

This study was approved by the Medical Ethical Committee of the Erasmus University Medical Center, Rotterdam, Netherlands, in accordance with the Dutch law on medical research in humans. Permit number MEC-2011-121.

### 2.2. Measurements of calcium score and calcium volume

Two different types of CT-scanner were used in this study. UMCG and EMC used Siemens Somatom Sensation 16 or 64 (Forchheim, Germany) and ASD used Philips Brilliance 40 or 64 (Eindhoven, The Netherlands). The calcium scores and volumes were retrospectively determined by two researchers, with Siemens software (Syngo.via® 2009–2012, serial number 100106, Siemens AG, Germany). The score was determined for the total aortoiliac trajectory starting from the T12-L1 disk space (just above the superior mesenteric artery) up to the internal iliac arteries, with a convolution kernel (CK) of 30f, slice thickness of 5 mm, and kV of 120 as described by Komen et al. [28,29]. The calcium score and

calcium volume were determined at a threshold level of 500 Hounsfield Units (HU) according to Komen et al. We used a higher threshold, than standard 130 HU, because of the intra-arterial contrast.

Calcium score and volume were determined on the CT-scan at 7 different segments in the aortoiliac trajectory. The presence of atherosclerotic plaques were computed at several segments: in the abdominal aorta (starting from vertebra T12-L1 up to the aortic bifurcation), the left and right common iliac arteries, the left and right internal iliac arteries, and the left and right external iliac arteries. These segments are representative for the entire aortoiliac trajectory and are important for the vascularisation of the colon and rectum. The vascularisation of the descending colon, sigmoid colon and rectum, which have an important role in the perfusion of the left-side anastomosis, partly arise from the inferior mesenteric artery (IMA). The origin of the IMA is at the ventral side of the abdominal aorta. The IMA is branching into the left colic artery, the sigmoid arteries, and the superior rectal artery. Vascularisation of the rectum originates from the superior, middle and inferior rectal arteries. The latter originates from the internal iliac artery (hypogastric artery) [30].

### 2.3. Statistical analysis

The statistical analysis was carried out using the Statistical Product and Service Solutions (SPSS Inc., Chicago, USA, version 20.0 for Windows). Univariate analysis between the groups with or without AL was done by the median and mean values of the Mann-Whitney *U* test or chi-square test. Data in the tables on the calcium score and volume are displayed in the original scale of measurement. However, these data were normalized by a logarithmic transformation prior to formal analysis. To determine whether there were significant differences between calcium score and calcium volume in relation to AL or no AL we performed multiple regression by generalized linear models. All reported *P* values were two-sided; a *P* value < 0.05 was considered to indicate statistical significance.

## 3. Results

In total 36 cases and 167 controls were included in the database, six cases and 62 controls were excluded from further analyses because they could not be matched properly, implicating 135 patients (30 cases and 105 controls) were included. The included patients are from all three hospitals, no significant differences between cases and controls between the centres. Table 1 illustrates the demographic, clinical, and operative characteristics of the included patients. Univariate analysis of the patient and operative characteristics showed significant differences in cardiac comorbidity and packed cell use during or after the operation between patients with or without AL. The mortality rate in the group with AL was not significantly different to the group without AL (*P* = 0.533; Table 2). Significant differences were found for postoperative bleeding, wound infection, postoperative ileus, intra-abdominal abscess, and urinary tract infection in the AL group, (*P* < 0.05; Table 2).

Table 3 presents the mean and standard deviation (SD) of the calcium score and calcium volume of the different trajectories. The measurements show that there is only one significant difference in one trajectory (right external iliac artery), indicating that patients without anastomotic leakage had a significant higher calcium volume in that specific trajectory.

Multiple regression analysis showed significant differences in the odds ratio for AL after higher calcium score in the right external iliac artery (Table 4). Negative odds ratio indicates a negative relationship between the probability of anastomotic leakage and the calcium score or calcium volume.

**Table 1**  
Patient and operation characteristics.

	(30 cases)	(105 controls)	<i>P</i> value
	Anastomotic leakage (%)	No anastomotic leakage (%)	
<b>Patient characteristics</b>			
Age (yrs)	64.50 ± 11.6	66.49 ± 11.4	0.412
Gender			0.508
Male	16 (53.3)	58 (55.2)	
Female	14 (46.7)	47 (44.8)	
BMI (kg/m <sup>2</sup> )	28.25 ± 6.7	26.88 ± 4.88	0.227
ASA score <sup>a</sup>			0.897
1	5 (19.2)	20 (20.6)	
2	16 (61.5)	62 (63.9)	
3	5 (19.2)	15 (15.5)	
4	0	0	
Comorbidity			
Cardiac comorbidity	9 (30.0)	14 (13.3)	<b>0.035</b>
Peripheral vascular disease	1 (3.3)	8 (7.6)	0.364
Diabetes Mellitus	3 (10)	12 (11.4)	0.563
Smoking (current) <sup>a</sup>	9 (33.3)	29 (30.9)	0.490
Medication			
Use of steroids	1 (3.3)	6 (5.7)	0.513
Use of statins <sup>a</sup>	5 (17.9)	13 (12.5)	0.324
Use of antihypertensiva <sup>a</sup>	10 (33.3)	39 (37.5)	0.424
Neoadjuvant radiotherapy	2 (6.9)	6 (5.7)	0.566
<b>Operation characteristics</b>			
Surgeon vs. resident	21 (70.0)	76 (73.1)	0.452
Type of operation			0.442
Sigmoid Resection	17 (56.7)	48 (45.7)	
Low Anterior Resection	7 (23.3)	32 (30.5)	
Rectosigmoid resection	3 (10)	15 (14.3)	
Hemicolectomy left	1 (3.3)	8 (7.6)	
Other	2 (6.7)	2 (1.9)	
Approach <sup>a</sup>			0.184
Laparotomy	22 (75.9)	68 (64.8)	
Laparoscopy	7 (24.1)	37 (35.2)	
Stapled vs. hand sutured <sup>a</sup>			0.098
Sutured	15 (51.7)	38 (36.2)	
Stapled	14 (48.3)	67 (63.8)	
Conversion <sup>a</sup>	5 (26)	14 (74)	0.205
Anastomotic configuration <sup>a</sup>			0.315
Side-end	5 (17.2)	31 (35.6)	
Side-side	5 (17.2)	10 (11.5)	
End-side	2 (6.9)	5 (5.7)	
End-end	17 (58.6)	41 (47.1)	
Stoma <sup>a</sup>	4 (14.3)	15 (17.9)	0.455
Packed cells <sup>a</sup>	25 (100)	36 (43.9)	<b>0.000</b>
Prophylactic drainage <sup>a</sup>	20 (69)	51 (49.5)	0.073

Bold values denote statistically significant *P* values (*P* < 0.05).

<sup>a</sup> The numbers do not add up to 135 because of occasional missing data.

#### 4. Discussion

Anastomotic leakage remains one of the most feared complications after colorectal surgery. There are several well-known risk factors for colorectal anastomotic leakage, such as high BMI,

advanced age, high level of comorbidity and a history of cardiovascular disease. All these risk factors are also correlated to atherosclerosis. However, atherosclerosis alone has not been identified as a risk factor for colorectal anastomotic leakage.

Sufficient tissue perfusion is an important factor for anastomotic healing. Several experimental and clinical studies have shown a correlation between a higher risk of AL when the oxygenation rate of the cut anastomotic edges did not rise during operation [31–34]. In these studies the oxygen saturation of the anastomosis was measured with different tools like near-infrared reflection spectroscopy or by custom-made electrodes. These studies conclude that perioperative low oxygen values lead to a higher risk of anastomotic leakage. Karliczek et al. used visible light spectroscopy to measure the oxygen values during colorectal surgery, they investigated that leaking anastomoses showed less rising oxygen values during operation than normal anastomoses [31].

This study had some limitations. Because of the retrospective design we could only include patients who preoperatively received a contrast enhanced abdominal CT-scan, this may have resulted in selection bias. Because of the heterogeneity of the group we matched the case and control patients to reduce any confounding.

**Table 2**  
Postoperative complications.

	(30 cases)	(105 controls)	<i>P</i> value
	Anastomotic leakage (%)	No anastomotic leakage (%)	
<b>Complications</b>			
Postoperative ileus	7 (23.3)	9 (8.6)	0.035
Dehiscence of laparotomy wound	2 (6.7)	3 (2.9)	0.308
Wound infection	7 (23.3)	5 (4.8)	0.005
Intra-abdominal abscess*	12 (40)	2 (1.9)	0.000
Urinary tract infection	2 (6.7)	0 (0)	0.048
Pneumonia	3 (10)	3 (2.9)	0.123
Bleeding	3 (10)	1 (1)	0.034
Mortality**	1 (3.3)	2 (1.9)	0.533

\* not close to anastomosis \*\* (<30days post-operative).

**Table 3**

Calcium volume and calcium score of the different trajectories 500 HU.

Trajectory	AL	n	Calcium volume			Calcium score		
			Mean	SD	P value	Mean	SD	P value
Total trajectory	yes	30	4.98	2.77	0.712	5.50	2.88	0.707
	no	104	4.75	2.95		5.26	3.12	
Aorta abdominalis	yes	30	4.42	2.85	0.561	4.93	2.93	0.713
	no	104	4.06	3.04		4.70	3.10	
Iliac artery								
Left common	yes	30	2.25	2.34	0.898	2.75	2.55	0.863
	no	104	2.18	2.42		2.65	2.76	
Right common	yes	30	2.86	2.35	0.112	3.36	2.62	0.697
	no	104	2.26	2.41		3.01	2.75	
Left internal	yes	30	1.12	1.72	0.109	1.49	2.12	0.412
	no	104	1.85	2.33		1.66	2.14	
Left external	yes	30	0.66	1.44	0.227	0.99	1.75	0.527
	no	104	1.32	2.09		1.34	2.17	
Right internal	yes	30	0.81	1.70	0.372	1.06	1.97	0.279
	no	104	1.12	1.67		1.50	1.96	
Right external	yes	30	0.69	1.67	<b>0.036</b>	0.93	1.91	0.159
	no	104	1.62	2.22		1.58	2.30	
Left and right common	yes	30	2.55	0.43	0.610	3.06	2.59	0.615
	no	104	2.22	2.42		2.83	2.76	
Left and right internal	yes	30	0.97	1.71	0.440	1.28	2.05	0.378
	no	104	1.49	1.00		1.58	2.05	

Bold values denote statistically significant P values ( $P < 0.05$ ).**Table 4**

Multiple regression by generalized linear models calcium volume and calcium score.

Trajectory	Calcium volume		Calcium score	
	Odds ratio	P value	Odds ratio	P value
500HU				
Total trajectory	0.03	0.710	0.03	0.704
Aorta	0.04	0.558	0.03	0.710
Left common iliac artery	0.01	0.897	0.01	0.862
Left internal iliac artery	−0.17	0.116	−0.04	0.694
Left external iliac artery	−0.25	0.117	−0.09	0.410
Right common iliac artery	0.10	0.227	0.05	0.524
Right internal iliac artery	−0.12	0.371	−0.12	0.279
Right external iliac artery	−0.25	0.043	−0.15	0.163
Left and right common iliac arteries	0.04	0.607	0.04	0.162
Left and right internal iliac arteries	−0.09	0.437	−0.08	0.376

The results of our study suggest that the abdominal calcium score and calcium volume in aortoiliac vessels are not correlated with anastomotic leakage in left-sided colon anastomoses. We did not find any indications that calcium measurements correlate to the onset of AL. Although, the collected data give a good reflection of reality because of the use of different CT-scanners in both local and university hospitals.

It is well known that left-sided anastomoses are associated with higher AL percentages when compared to more proximal anastomoses [35,36]. However, in this study we showed that the calcium scores in the atherosclerotic plaques of patients with AL, are not higher than in patients without AL for the same type of surgery. The only negative odds correlation for anastomotic leak was a lower calcium volume in the right external iliac artery, we do not have a rational explanation for this, this is probably a coincidence.

Our results are in line with previous research by Kornmann et al., who scored the stenosis caused by arteriosclerotic lesions in the visceral arteries. They studied 242 patients who underwent colorectal anastomosis. The authors suggested that asymptomatic visceral artery occlusive disease is not a risk factor for anastomotic leakage [37]. This may be due to the presence of a developed collateral network [38].

Komen et al. investigated that patients with higher calcium scores in the common iliacal arteries had an increased leakage risk of colorectal anastomosis. This study also mentioned that the calcium score of the left internal iliac is significantly higher in patients

with colorectal AL, however the reason for this finding remained unclear [28].

In this present study we used the same measurement method of the calcium score as described by Komen et al. [28]. In the current study we could not measure the calcium mass, due to the lack of software support on this value for the different types of CT-scanners. Although the calcium volume and calcium score correlate very well with the calcium mass, Komen et al. showed a better correlation between the calcium mass and AL than the calcium score and AL [28]. It is possibly due to the smaller study population in Komens's study.

Measuring the calcium volume and calcium score with a threshold of 500HU is higher than usual because of the contrast enhanced CT scan. Because of the intra-arterial contrast we probably missed some calcifications but this is the same in the AL group as in the non-AL group. This will not have any influence on the results. This will also explain the low scores of calcium mass and calcium volume compared to other studies.

From the results obtained in this study, we conclude that abdominal atherosclerotic calcifications expressed as calcium score and calcium volume are not useful for preoperative risk assessment for left-sided anastomoses. This study indicates that calcified atherosclerosis in the large abdominal arteries does not influence the perfusion of the anastomotic edges. It is known that coronary calcified plaques represents approximately 20% of the total plaque, the other 80% is lipid-rich plaque or fibrous plaque [23]. This may indicate that the calcified plaques are not representative enough for the total atherosclerosis in the abdominal arteries.

Future research regarding the relationship between abdominal atherosclerosis and the risk of colorectal anastomotic leakage should concentrate on the relationship between abdominal calcifications and the severity of abdominal artery lumen stenosis and the perfusion of the colon during surgery. Furthermore, visualization of the collateral network around the anastomosis may provide extra information on the onset of ischemia leading to AL.

## 5. Conclusion

This study demonstrates that the abdominal calcium score and calcium volume in the aortoiliac territory are not correlated with



anastomotic leakage in left-sided colon anastomosis.

### Ethical approval

Yes, MEC2011-121.

### Sources of funding

None.

### Author contribution

J.F.L., J.J., G.J.K., K.A.V. and G.S.A.B. designed the research; G.S.A.B., K.A.V., M.C.J.M., P.M.A.O., and K.H. performed the research; G.S.A.B. analyzed the data; G.S.A.B., K.A.V., and J.F.L. wrote the article, and all authors drafted the article or revised it critically for important intellectual content and approved the current version.

### Conflicts of interest

No conflicts of interest.

### Guarantor

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### Acknowledgment

None.

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